Expression of cadherins and CD44 isoforms in ovarian endometrial cysts

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We evaluated the immunohistochemical expression of cadherins and CD44 variants in 20 endometriomas, 20 cystadenomas, 20 borderline ovarian tumours as well as 20 ovarian carcinomas, and the serological and cystic fluid concentrations of soluble E-cadherin and soluble CD44 standard (sCD44sdt) in 20 endometriomas, 20 cystadenomas, six borderline and 11 carcinomas of the ovary. In endometriomas, immunostaining of E- and N-cadherin was negative (20 and 30% respectively). CD44 H, v3 and v6 immunostaining were detected in 63, 10 and 40% respectively. A difference in immunostaining for E-cadherin was found between endometriomas and cystadenomas (P < 0.001) and for N-cadherin between endometriomas and carcinomas (P < 0.001). A difference in CD44H immunostaining was observed between endometriomas and cystadenomas (P < 0.035) but not with borderline ovarian tumours and carcinomas. No difference in serum concentrations of soluble E-cadherins and CD44 standard was found between the four groups of tumours. Cystic fluid concentrations of E-cadherin were lower in endometriomas than in borderline tumours and ovarian carcinomas (P < 0.001). High concentrations of soluble CD44 standard cystic fluid were found in endometriomas than in other ovarian cysts. Endometriomas and borderline tumours share alterations of cadherins and CD44 isoforms which may help in the understanding of the aggressive and invasive potentials of endometriotic cells. Key words: adhesion molecules/cadherins/CD44/endometriomas/ovarian tumours

Introduction

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterus. Several authors estimated that ~10% of women in their reproductive period develop endometriosis (Barbieri, 1990; Jimbo et al., 1997). Furthermore, in infertile women, endometriosis is found in 30–40% of patients (Battista et al., 1991). Endometriotic lesions are mostly found in the pelvic peritoneum and ovary with formation of endometriomas which are cystic tumours containing chocolate fluid. Endometriomas grow progressively and invasively in an oestrogen-dependent manner, and are a cause of dysmenorrhea, dyspareunia, pelvic pain and infertility (Spuijbroek et al., 1992; Gaetje et al., 1995). Local evolution of endometriomas is characterized by a high risk of recurrence and the possibility of implantation at distant sites and invasion of host tissues (Sampson, 1927) suggesting that they share characteristics similar to those found in premalignant tumours such as borderline tumours and in malignant ovarian lesions.

Abnormal expression of structural adhesion molecules such as cadherins, integrins, and CD44 proteins by neoplastic cells is likely to be an important determinant of local invasion and dissemination (Frixen et al., 1991; Takeichi, 1993). Cadherins are members of a family of transmembrane glycoproteins that mediate cell–cell adhesion by homophylic recognition in a calcium-dependent manner. Alterations in cadherin function might result from either qualitative or quantitative abnormalities. In many examples of carcinomas, the occurrence of altered cadherin expression has been correlated with low histological differentiation, increased risk of local invasion and metastatic disease, and poor prognosis (Shimoyama et al., 1989; Shiozaki et al., 1991; Inoue et al., 1992; Gamallo et al., 1993; Darat et al., 1997). In normal endometrial tissue, monolayer cultures showed that only a low number of epithelial cells are E-cadherin negative and were never found to invade collagen gels (Gaetje et al., 1997). In contrast, E-cadherin negative epithelial cells from peritoneal endometriosis biopsies were invasive in vitro. Furthermore, primary cells from human endometriotic lesions were invasive in an in-vitro collagen assay to an extent comparable to that of metastatic carcinoma cells (Gaetje et al., 1995). Therefore, the lack of E-cadherin expression seems to be crucial in the invasive phenotype of endometriotic cells. Little is known about E-cadherin expression in vivo of endometriotic biopsies. Van der Linden et al. (1994) reported that sections of eutopic endometrium were E-cadherin positive, whereas six out of eight sections of endometriotic biopsies were E-cadherin negative.

CD44 proteins are heavily glycosylated transmembrane proteins, involved in cell–cell and cell–matrix interactions. All CD44 proteins are encoded by a single gene and are produced by alternative splicing. Various clinical and experimental studies have suggested that the abnormal expression of CD44 variant proteins may help in the identification of the neoplastic and preneoplastic characteristics of epithelial cells (Matsumara et al., 1992; Heider et al., 1993; Ishii et al., 1993) and is associated with tumour burden, progression and metastatic dissemination (Matsumara et al., 1992; Uhl-Steidl et al., 1995). Furthermore, in ovarian carcinomas CD44 isoform expression...
is associated with peritoneal spreading (Cannistra et al., 1993; Jones et al., 1995). Nevertheless, to date few reports have been published regarding CD44 expression in endometrial tissue. Fugita et al. (1994) reported that normal endometrial cells express standard and variant forms of CD44 proteins. However, no data exist for the expression of CD44 in endometriotic lesions.

Cell adhesion molecules exist in two forms: a membrane form, detectable on the cell surface, and a soluble form, detectable in the serum and in biological fluids. In oncology, the adverse prognostic value of elevated circulating concentrations of E-cadherin and CD44 is underlined (Katayama et al., 1994). In the same way, elevated concentrations of soluble adhesion molecules in biological fluids in contact with neoplastic cells have proven to be of diagnostic and prognostic value in cancers of the bladder and the stomach (Guo et al., 1994).

We were therefore prompted to analyse the immunohistochemical expression of E- and N-cadherins, CD44 H, and isoforms V3 and V6 in a series of endometriomas. For this purpose, formalin-fixed, paraffin embedded tissue was used. In addition, we evaluated the concentration of E-cadherin and CD44 standard soluble forms in serum and cystic fluid of patients with endometriomas.

Our aims were to evaluate: (i) the immunohistochemical expression of E and N-cadherins and CD44 isoforms in endometriomas as compared with cystadenomas, borderline tumours and carcinomas of the ovary, (ii) the serum and cystic fluid concentrations of E-cadherin and CD44 isoforms in endometriomas as compared with those found in patients with cystadenomas, borderline tumours and carcinomas of the ovary.

Materials and methods

Materials

Tissue samples from ovarian tumours were obtained from 80 patients, treated at the Service de Gynécologie de l’hôpital Bichat-claude Bernard. Histological typing was performed according to the Oncology Committee of the International Federation of Gynecology and Obstetrics (FIGO, 1987). The study group comprised 20 cases of endometriomas and 60 cystic ovarian lesions (20 cystadenomas, 20 borderline tumours and 20 ovarian carcinomas). Each group of cystadenomas, borderline ovarian lesions and ovarian carcinomas included 10 mucinous and 10 serous tumours. In addition, for immunohistochemical analysis, four normal ovarian tissue samples were obtained.

Serum samples were obtained immediately before surgery, and cystic fluid samples by cyst puncture after removal of lesions in 18 patients with endometriomas and in 38 patients with cystic ovarian lesions including 20 cystadenomas (16 serous and four mucinous tumours), seven borderline tumours (six serous and one mucinous tumour) and 11 ovarian carcinomas (seven serous, three endometriotic and one mucinous cancer).

The mean age of patients with endometriomas was 31.5 years (range 24–40). Among the 20 patients, 10 (50%) complained of pelvic pain and dysmenorrhea, nine (45%) of infertility and one (5%) of both pelvic pain and infertility. The mean sonographic size of endometriomas was 50 mm (range 20–110). All patients were treated by laparoscopic cystectomy. Endometriosis was classified according to the revised American Fertility Society (AFS) scoring (AFS, 1985). Four out of 20 patients (20%) had bilateral endometriomas and 13 out of 20 patients (65%) presented with peritoneal endometriosis lesions. Among the 20 women, 11 (55%) had stage III rAFS and nine (45%) had stage IV. The mean rAFS score was 38.5 (range 20–92). Six out of 20 patients (30%) had a recurrence of endometriosis.

Methods

Antibodies

The antibody against E-cadherin was the monoclonal mouse antibody HECD-1 (R&D Systems, Abingdon, UK). To detect N-cadherin, we used a commercially available rabbit polyclonal antibody raised against the C-terminal amino acid sequence of chicken N-cadherin (Sigma, St Louis, MO, USA). The monoclonal antibodies (R&D Systems, Abingdon, UK) used in the study were: 2C5, binding to CD44s and all the variants encoded by exons 3–10; 3G5, specific for CD44v3; and 2F10, specific for CD44v6.

Immunohistochemical technique

In all cases, 3 µm thick paraffin embedded sections of formalin fixed tissue samples were used. Sections were deparaffinized and rehydrated through a series of graded ethanol solutions and were incubated in methanol containing 0.3% hydrogen peroxide (H2O2) to inhibit endogenous peroxidase. For antigen unmasking, sections were incubated in 10 mM citrate buffer, pH 6, in a microwave oven for three periods of 5 min each at 500 W. After washing, sections were incubated for 1 h at room temperature with the primary antibody in appropriate dilution. Visualization was performed using the avidin–biotin technique (Vector Laboratories, Burlingame, UK). Peroxidase activity was detected according to the method of Graham and Karnovsky (1966). Negative controls were obtained by omitting the primary antibody, substituted by either phosphate-buffered saline or isotypic immunoglobulins. All controls were negative.

Analysis of immunohistochemical results

The percentage of positive cells was evaluated on 10 consecutive high magnification power fields (×40) by two observers. Mean values were obtained by averaging 10 counts per tissue section. In accordance with previous studies (Inoue et al., 1992; Darai et al., 1997), for E- and N-cadherins, tumours were considered positive when more than 90% of tumour cells were labelled and negative when less than 10% of tumour cells were labelled.

Assay for soluble adhesion molecules in serum and cystic fluid samples

Commercially available ELISA kits were used for the determination of soluble E-cadherin (Takara, Kyoto, Japan) and soluble CD44 standard (BenderMed, Vienna, Austria) in serum and cystic fluid samples. This technique was performed essentially according to the manufacturers’ instructions in 20 endometriomas, 20 cystadenomas, seven borderline ovarian tumours and 11 ovarian carcinomas. Briefly, test standards and plasma samples were incubated for 90 min with the provided peroxidase-conjugated primary antibody solution. After substrate incubation with orthophenylenediamine for soluble E-cadherin or tetramethylbenzidine for soluble CD44 standard, the enzyme reaction was stopped and the optical density was measured photometrically at, respectively 492 and 450 nm. The concentrations of immunoactive soluble E-cadherin and soluble CD44 standard, expressed in ng/ml, were determined using a standard curve. All assays were performed in duplicate and the mean was taken for all further analyses.

For ovarian cysts, aliquot fractions of 25 µl of cystic fluid were found to be sufficient to provide reliable results. We verified that the intra-assay coefficient of variation for samples or cystic fluid assayed in replicates of 10 was between 4.1 and 6.5% and the inter-assay coefficient of variation for samples of cystic fluid assayed in duplicate
by two operators was between 8 and 14.5%. These figures compared well with those given by the manufacturers for serum samples. Normal serum values (mean $\pm$ SD) previously determined in our laboratory for healthy subjects were: 2900 $\pm$ 510 ng/ml for soluble E-cadherin and 470 $\pm$ 110 ng/ml for soluble CD44 standard.

**Statistical analysis**

For statistical evaluation, Fisher’s exact test, Wilcoxon two-sample test and Spearman-rank correlation test were used. A $P$ value $< 0.05$ was considered significant.

**Results**

**Immunohistochemistry**

Immunohistochemical detection of E- and N-cadherins and CD44 isoforms in normal ovarian tissue

E- and N-cadherins were detected along the lateral membranes of epithelial cells. The endothelial lining of ovarian vessels and a majority of stromal cells showed staining for the monoclonal antibody 2C5, directed to all CD44 isoforms. A few epithelial cells scattered in the germinial epithelium showed membrane staining. CD44 v3 and CD44 v6 were not detected in the germinial epithelium of the normal ovary.

Immunohistochemical detection of cadherins in ovarian tumours

At a cellular level, E- and N-cadherins were detected along the lateral membranes of lining epithelial cells (Figures 1a, c).

E-cadherin immunostaining was negative in four out of 20 cases of endometriomas (20%). In comparison, none of 20 cases of cystadenomas, four out of 20 cases of borderline tumours (20%) and six out of 20 cases of carcinomas (30%) were E-cadherin negative.

The mean $\pm$ SD of tumour cell E-cadherin positive in endometriomas, cystadenomas, borderline tumours and carcinomas are summarized in Table I. The difference was statistically significant between the four groups of tumours ($P < 0.001$). No statistically significant difference in immunostaining was noted between endometriomas and borderline tumours and between endometriomas and ovarian carcinomas. In contrast, a statistically significant difference in E-cadherin expression was found between endometriomas and cystadenomas ($P < 0.001$).

N-Cadherin immunostaining was positive in 14 out of 20 cases of endometriomas (70%). In comparison, 15 out of 20 cases of cystadenomas (75%), 12 out of 20 cases of borderline tumours (60%) and none of 20 of carcinomas were N-cadherin positive.

The mean $\pm$ SD of E-cadherin positive staining observed in endometriomas, cystadenomas, borderline tumours and carcinomas are summarized in Table I. The difference was statistically significant among the four groups of tumours ($P < 0.001$). The difference was statistically significant between endometriomas and carcinoma ($P < 0.001$). No statistically significant difference in N-cadherin staining was found among the three groups of endometriomas, cystadenomas and borderline tumours of the ovary.

Immunohistochemical detection of CD44 isoforms in ovarian tumours

CD44 antigens were preferentially expressed along the basolateral domain of the plasma membrane of polarized cells. An expression over the whole surface of epithelial cells was frequently detected in endometriomas (Figure 1b), but also in borderline tumours (Figure 1d) and in ovarian carcinomas. The proportion of positive cells was variable according to the case and to the type of tumour.

CD44 H immunostaining analysis was available in 19 out of 20 cases of endometriomas. CD44 H immunopositivity was detected in 12 cases of endometriomas (63%). In contrast, immunostaining for the CD44 H was detected in 12 out of 20 cases of cystadenomas (60%), in 18 out of 20 cases of borderline tumours (90%) and in 19 out of 20 cases of carcinomas (95%).

The mean $\pm$ SD of tumour cells CD44 H positive in endometriomas, cystadenomas, borderline tumours and ovarian carcinomas are shown in Table I. The difference was statistically significant between the four groups of tumours ($P < 0.001$). A difference in CD44 H immunostaining was observed between endometriomas and cystadenomas ($P < 0.035$). In contrast, no statistical difference in immunostaining was noted between endometriomas and borderline tumours and between endometriomas and ovarian carcinomas.

CD44 v3 immunostaining was detected in two out of 20 cases of endometriomas (10%). In comparison, none of the 20 cystadenomas cases, six out of 20 borderline tumour cases (30%) and seven out of 20 carcinoma cases (35%) were CD44v3 positive.

The mean $\pm$ SD of tumour cells CD44 v3 positive in endometriomas, cystadenomas, borderline tumours and ovarian carcinomas are presented in Table I. The difference was statistically significant between the four groups of tumours ($P < 0.04$). A difference in CD44 v3 immunostaining was noted between endometriomas and ovarian carcinomas ($P < 0.025$). No difference in CD44 v3 immunostaining was observed between endometriomas tumours and the groups of cystadenomas and borderline tumours.

CD44 v6 immunostaining was detected in eight out of 19 cases of endometriomas (40%). In comparison, three out of 20 cases of cystadenomas (15%), eight out of 20 cases of borderline tumours (40%) and five out of 20 cases of carcinoma (25%) were CD44v6 positive. No statistically significant difference in CD44 v6 staining was noted between the four groups of lesions.

**Serum and cystic fluid determination**

Serum and cystic fluid concentrations of soluble E-cadherin in ovarian tumours

The serum and cystic fluid concentrations of soluble E-cadherin in endometriomas, cystadenomas, borderline tumours and carcinomas of the ovary are given in Tables II and III. No statistically significant differences in soluble E-cadherin serum concentrations were found between the four groups of tumours.

The mean cystic fluid concentration of soluble E-cadherin was significantly higher in endometriomas than in cystadenomas ($P < 0.0001$). In addition, soluble E-cadherin cystic fluid concentration was significantly lower in endometriomas than in both borderline tumours ($P < 0.001$) and in ovarian carcinomas ($P < 0.008$).
Cadherins and CD44 expression in endometriomas

Figure 1. Expression of E-cadherin and CD44 variant isoforms in ovarian tumours. (a) and (e) show representative examples of E-cadherin immunostaining in an endometrial cyst (a) and in a benign mucinous tumour (e) with HECD-1 antibody. E-cadherin is detected along the lateral membranes of epithelial cells. (b) and (d) show the reactivity of cells in an endometrial cyst (b) and in a borderline mucinous tumour (d) with 2C5 antibody directed against all CD44 variant isoforms. The labelling is membranous and is restricted to the basal and lateral domains of the plasma membrane. Immunoperoxidase with nuclear countercolouration with Harris’ haematoxylin. Original magnification ×80. Bar = 100 µm.

Table I. Immunohistochemical expression of CD44 H, v3, v6 isoforms, and E- and N-cadherins in endometriomas, cystadenomas, borderline tumours and carcinomas of the ovary (percentage of tumour cells positive)

<table>
<thead>
<tr>
<th></th>
<th>Endometriomas mean % ± SD</th>
<th>Cystadenomas % ± SD</th>
<th>Borderline tumours % ± SD</th>
<th>Carcinomas % ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44 H</td>
<td>60 ± 50</td>
<td>30 ± 30</td>
<td>50 ± 30</td>
<td>60 ± 30</td>
</tr>
<tr>
<td>CD44 v3</td>
<td>0</td>
<td>0 ± 20</td>
<td>0 ± 20</td>
<td>30 ± 20*</td>
</tr>
<tr>
<td>CD44 v6</td>
<td>20 ± 30</td>
<td>10 ± 20</td>
<td>10 ± 20</td>
<td>20 ± 10</td>
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<tr>
<td>E-Cadherin</td>
<td>60 ± 40</td>
<td>90 ± 10*</td>
<td>60 ± 40</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>N-Cadherin</td>
<td>70 ± 50</td>
<td>90 ± 20</td>
<td>80 ± 30</td>
<td>30 ± 20*</td>
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SD = standard deviation.

*Difference statistically significant with the other three groups of ovarian tumours.

Serum and cystic fluid concentrations of soluble CD44 standard in ovarian tumours

The serum and cystic fluid concentrations of soluble CD44 standard in endometriomas, cystadenomas, borderline tumours and carcinomas of the ovary are given in Tables II and III. No statistically significant differences in soluble CD44 standard serum concentrations were found among the four groups of tumours.

The mean cystic fluid concentration of soluble CD44 standard was significantly higher in endometriomas than in cystadenomas (P < 0.0001). In addition, soluble CD44 standard cystic fluid concentrations in endometriomas were significantly higher than those found in borderline tumours (P = 0.01) and in carcinomas of the ovary (P = 0.008).

No statistically significant correlation was found between
concentrations in serum and cystic fluid samples of soluble E-cadherin and soluble CD44 standard in the same patient, irrespective of the type of tumour.

**Discussion**

Our study shows that at least two cadherins are expressed in endometriomas, namely E-cadherin and N-cadherin. In endometriomas, a lack of E-cadherin expression was observed in 20% of cases. These results are in accordance with those of Van der Linden *et al.* (1994), who reported that sections of peritoneal endometriotic biopsies were more frequently E-cadherin negative (six out of eight cases), whereas sections of eutopic endometrium were constantly E-cadherin positive. Moreover, Gaetje *et al.* (1997) found that E-cadherin negative epithelial cells from peritoneal endometriosis biopsies are invasive *in vitro*, whereas no invasive behaviour was noted in E-cadherin positive epithelial cells. The occurrence of alterations in cadherin is of particular interest because two main theories have been formulated to explain the pathogenesis of endometriosis (Sampson, 1927; Fujii, 1991): the transportation theory and the metaplasia theory. The transplantation theory implies that endometrial cells must have the capability to detach from the endometrium, re-attach after passive transport into the peritoneum and invade the host tissues. This hypothesis is in accordance with previous studies (Van der Linden *et al.*, 1994, 1995) which reported that endometrial samples expressed E-cadherin, in contrast to epithelial cells in menstrual effluent where E-cadherin expression was detected in lower amounts. The metaplasia theory requires invasive mechanisms for the establishment of endometriotic lesions beneath the peritoneal surfaces. According to the metaplasia theory, endometriotic cells could be derived from the peritoneum or the coelomic epithelium, which expresses only low concentrations of E-cadherin (Gaetje *et al.*, 1997). Moreover, it has been recently shown that mesothelial cells express N-cadherin (Hatta *et al.*, 1997; Peralta Soler *et al.*, 1995). The expression of N-cadherin by endometriotic cells is more unexpected. Indeed, N-cadherin is usually regarded as a characteristic of neural and muscular cells (Takeichi, 1993). In our experience, the absence of N-cadherin expression was found in 30% of endometriomas. This is of particular interest because, in accordance with a previous study (Peralta Soler *et al.*, 1997), it is possible to speculate that the expression of N-cadherin by endometriotic cells of the ovary may be of metaplastic origin.

Other cell adhesion molecules may play a role in the development of endometriomas. In the present study CD44*H* immunostaining over the whole surface of endometriotic cells from the ovary was frequently detected (63% of cases). In the same way, we found a low expression of CD44 variants v3 and v6. Experimental studies have suggested that CD44 variants may play a crucial role in the peritoneal spreading and invasiveness of malignant ovarian epithelial cells (Cannistra *et al.*, 1995; Uhl-Steidl *et al.*, 1995). Therefore, these results suggest that the loss of cell adhesion properties may play a role in the shedding of endometrial tissue during menstruation and in the attachment of endometrial tissue fragments to the peritoneum.

Although the histogenesis of endometriomas is different from that of other ovarian tumours, it is interesting to note that endometriotic lesions share some clinical features with the borderline tumours and carcinomas of the ovary such as recurrence of the disease, invasion of host tissues and peritoneal spreading. In the present study, no differences in E-cadherin expression were observed between endometriomas and both borderline tumours and ovarian carcinomas. Furthermore, a similar strong expression of N-cadherin was found in both endometriomas, cystadenomas and borderline tumours of the ovary. In contrast, a decrease in N-cadherin expression was noted in ovarian carcinomas. Finally, our results suggest that endometriomas have expression of cadherins similar to that found in borderline tumours. These facts may be indicative of neoplastic potentiality for endometrial ovarian cysts. This concept is reinforced by recent reports (Nilbert *et al.*, 1995;
Jimbó et al., 1997) indicating that endometrial cysts are monoclonal in origin which is consistent with neoplastic features (Fialkow, 1976; Nowell, 1976). Moreover, Jiang et al. (1996) demonstrated loss of heterozygosity at candidate ovarian tumour suppressor gene loci in 28% of endometriotic ovarian lesions on chromosomes 9p, 11q and 22q supporting the notion that tumour suppressor gene inactivation may play a role in the development of at least a subset of cases.

In our experience, the expression of adhesion molecules such as CD44 isoforms was similar in endometriomas to borderline tumours, and consequently may play a role in the aggressiveness of ovarian endometriotic cells. These data are in line with those of previous studies which found that the overexpression of the cell surface hyaluronan receptor CD44 H or alternatively spliced variants of CD44 were associated with aggressiveness or metastatic behaviour in a variety of human tumours (Cannistra et al., 1993). This is supported by the findings that CD44 has a role in tumour cell motility in vitro and enhances tumour growth and metastasis in vivo models (Sy et al., 1991). CD44 and extracellular matrix proteoglycan hyaluronan interaction appears to be a key aspect of CD44 function and is required for tumour development. Therefore, properties of CD44 isoforms may explain the invasive behaviour of ovarian endometriotic lesions.

In our experience, no serum concentration elevation in soluble E-cadherin and CD44std was observed in patients with endometriomas as compared with patients presenting other cystic ovarian tumours. Therefore, soluble adhesion serum determination has no diagnostic relevance for endometriotic ovarian tumours.

Elevated cystic fluid concentrations of soluble E-cadherin are detected in endometriomas as compared to cystadenomas. Moreover, soluble E-cadherin concentrations in endometriomas were significantly lower than those found in borderline and in malignant ovarian tumours. Therefore, the determination of soluble E-cadherin in cystic fluid had diagnostic relevance for ovarian tumours.

High concentrations of soluble CD44 standard were found in endometriomas and were significantly greater than those noted in cystadenomas, borderline tumours and in ovarian carcinomas. These results point to the possible role of CD44 isoform protein in the pathogenesis of endometriosis.

In conclusion, the results of our study support the proposal that adhesion molecules are implicated in the development of ovarian endometriotic lesions. Moreover, the fact that endometriomas share some characteristics of premalignant ovarian tumours such as borderline tumours and malignant tumours of the ovary, especially alteration of E-cadherin and CD44 expression, suggests a crucial mechanism in the understanding of the aggressive and invasive potentials of the endometriotic cells.

References
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